Understanding the Immunological Basis of the Medical Revolution Occurring in Cancer

Immunotherapy: Implications for Ultrasound, Radiation and Other Biophysical Therapies.

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Current strategies to combat cancers

Mechanics -- surgery, 1600BC
Physics -- radiotherapy, 1896
Chemistry -- chemotherapy, 1942
Biology -- immunotherapy, ~ mid-1970s

Immunotherapy is currently undergoing a period of remarkable therapeutic success. The resultant “medical revolution” has implications for how and if all other therapies, including biophysical therapies, will be applied in the future.
Tumor Antigens Exist and are Immunogenic

Tumor-specific: TSA
- Oncogenic mutants of normal cellular genes: ras, bcr-abl, p53
- Randomly mutated genes: TSTA's (tumor-specific transplantation antigens)
- Can be identified: biochemical, cDNA cloning

Tumor-associated: TAA
- Normal cellular proteins aberrantly expressed
- Tyrosinase - melanomas (enzyme melanin biosynthesis)
- Cancer/testis antigens: expressed testis and trophoblasts
- Oncofetal antigens: developing fetal tissue
- CEA: carcinoembryonic antigen - colo and many cancers,
- AFP: α-fetoprotein - hepatocellular cancer and others
- Not specific; can be induced inflammatory conditions
- Altered glycolipid and glycoprotein antigens: gangliosides
- Mucin 1 - O-linked carbohydrates
- Tissue-specific differentiation antigens

Immunotherapy (& Immunology) at the Center Stage of Cancer Therapy

- FDA approvals: Provenge, CTLA4 blockade, PD1/PDL1 blockers
- Big Pharma & Biotech Enter Cell-based Immunotherapies (DC, CAR-T, TIL...)
- 2013 Science Breakthrough of the Year, Time Magazine Cover Story, April 4th, 2016
- 2011 Nobel Prize: Ralph Steinman (Dendritic cell function)
- 2015 Lasker Award: James Allison

Survival with nivolumab significantly better vs. docetaxel in patients with previously treated squamous-cell NSCLC.

P < 0.001
Brahmer et al, NEJM 2015
Original 6 Hallmarks of Cancer—no mention of a role for evasion of immunity!

Hanahan & Weinberg Cell 2000

Hallmarks of Cancer - The Next Generation
-2011

Emerging Hallmarks

Demolishing cellular energetics

Avoiding immune destruction

Genome instability and mutation

Tumor-promoting inflammation

Enabling Characteristics

Hanahan & Weinberg Cell 2011

Tumor-infiltrating lymphocytes-
Correlation with survival
in ovarian cancer patients

Zhang et al. NCIAM 214: 203-205, 2003
Cancer classification using the “Immunoscore”: a worldwide task force

- Currently histopathological stage scoring is based on TNM (Tumor, Node, Metastasis)
- Patients of same stage can have very different outcomes
- Little value in predicting response to therapy
- Long-term outcome involves immune response
- “Immunoscore” = immunological biomarker


Different immune cell infiltrates are associated with good or poor prognosis

The Immune Contexture

Immunotherapy: Many approaches currently in progress

- Checkpoint Inhibitors ✔
- Oncolytic Viruses ✔
- Bi-specific Antibodies ✔
- Cancer Vaccines ✔
- CAR-T ✔
- Natural Killer Cell ✔
- T-cell Receptors ✔

- DART
- STING
- Cytotoxic T-cells
- Tumor Infiltrating Lymphocytes
- Cytokines
- More.....

✔ = FDA Approved
The challenges: Even though immunotherapy is resulting in remarkable outcomes in deadly cancers, only a subset of patients respond. And, some cancers appear more resistant than others. Also, the toxicity (immune adverse effects) can be significant in many patients.

Some basic tumor immunology leading to the current immunotherapies:

Can Radiation, Chemotherapy, HIFU, RF Ablation be used to improve outcome of Immunotherapy?

Some Basic Concepts

• The immune system can result in long lasting protection against many diseases.
• T Lymphocytes are particularly important for this long lasting memory against disease.
• Some pathogens, and cancer cells, have learned to escape the immune response.
• Cancer represents a dynamic equilibrium with the immune system. Influencing that balance can result in either long lasting cure, or progression of cancer.

A fundamental experiment which still drives the field of tumor immunology.....

For Background and Historical context: William Paul: A textbook of Immunology (Chapter on Tumor Immunology by Hans Schreiber, Univ. of Chicago)
The immune status of mice is a critical determinant of their susceptibility to tumors induced by chemical carcinogens.  

R. D. Schreiber et al. Science 2011;331:1565-1570  
Published by AAAS


T cells control latent tumors


Advantages of T Cell-Based Cancer Immunotherapy

1. Exquisite specificity for target; limit collateral damage.  
2. Target non-resectable tumors.  
3. T cells can target tumors at sites throughout the body.  
4. Long-lasting protection = Immunological Memory
Tumor Draining Lymph Node

Adaptive Tumor Immunity:

1. T cell recognition of tumor Ags
2. High frequency of tumor-specific T cells
3. T cell trafficking to lymph nodes & tumors

The Cancer-Immunity Cycle

Chen and Mellman Immunity 39; 2013
Mechanisms of Tumor Escape from Immune Responses

- Loss of MHC or TAP
- Loss of co-stimulatory molecules
- Antigenic variation
- Secretion of immunosuppressive factors
  - e.g. TGF-b, IL-10
- T cells don’t penetrate solid tumors
- Exhaustion of T cells
- T regulatory cells suppress anti-tumor responses


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**Immunotherapy:**

**Checkpoint inhibitors**

- Immune system relies on multiple checkpoints to avoid over activation on healthy cells
- Tumor cells hijack these checkpoints to escape detection
- CTLA-4 & PD-1 are upregulated on T cell surface in some cancers
- PD-L1 can be expressed on tumor cells endogenously or induced by association with T cells
- PD-1:PD-L1 interaction results in T cell suppression (anergy, exhaustion, death)
In the coming years, we are likely to see the continued expansion of the therapeutic landscape of immune-checkpoint inhibitors, targeted therapies, and novel companion and complementary diagnostics, including the further development of multiplex genomic testing platforms (including novel tissue-based or blood-based assays).
CAR T cell transfer immunotherapy

Cytotoxicity of CD19-specific CAR-expressing T Lymphocytes against B Cell Lymphoma

1st, 2nd, and 3rd generation CARs
The starting line for testing new therapies is changing fast...implications for new therapies?

FROM THE ANALYST’S COUCH
The SCCHN drug market
April 2017

The power of adaptive immunity in the response to chemotherapy

Obeid et al, Nature Medicine, 2007

And, specifically the role of CD8+ T lymphocytes

Obeid et al, Nature Medicine, 2007
Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment
Ralph R. Weichselbaum and colleagues: University of Chicago
2009 114: 589-595

Developments in RT technology allow for the use of high-dose (or ablative) RT to target local tumors, with limited damage to the surrounding normal tissue. We report that reduction of tumor burden after ablative RT depends largely on T-cell responses. Ablative RT dramatically increases T-cell priming in draining lymphoid tissues, leading to reduction/eradication of the primary tumor or distant metastasis in a CD8+ T cell-dependent fashion. We further demonstrate that ablative RT-initiated immune responses and tumor reduction are abrogated by conventional fractionated RT or adjuvant chemotherapy but greatly amplified by local immunotherapy. Our study challenges the rationale for current RT/chemotherapy strategies and highlights the importance of immune activation in preventing tumor relapse. Our findings emphasize the need for new strategies that not only reduce tumor burden but also enhance the role of antitumor immunity.

The Cancer-Immunity Cycle
Chen and Mellman Immunity 39; 2013

New paradigms concerning outcome from radiation therapy
Ionizing radiation acts as a modifier of the tumor microenvironment converting the tumor into an in situ vaccine.

Demaria & Formenti: Frontiers in Oncology, 2012

Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice


Here we describe a treatment strategy that combines PDT by a new chlorin-based nanoscale metal–organic framework (nMOF), TBC-Hf, and a small molecule immunotherapy agent that inhibits indoleamine 2,3-dioxygenase (IDO), encapsulated in the nMOF channels to induce systemic antitumor immunity. The synergistic combination therapy achieved effective local and distant tumor rejection in colorectal cancer models. We detected increased T cell infiltration in the tumor microenvironment after activation of the immune system with the combination of IDO inhibition by the small-molecule immunotherapy agent and immunogenic cell death induced by PDT. We believe that nMOF-enabled PDT has the potential to significantly enhance checkpoint blockade cancer immunotherapy, affording clinical benefits for the treatment of many difficult-to-treat cancers.

Chlorin-Based Nanoscale Metal–Organic Framework Systemically Rejects Colorectal Cancers via Synergistic Photodynamic Therapy and Checkpoint Blockade Immunotherapy

Kuangda Lu †§, Chunbai He †§, Nining Guo †‡§, Christina Chan †, Kaiyuan Ni †, Ralph R. Weichselbaum ‡, and Wenbin Lin * † J. Am. Chem. Soc., 2016, 138 (38), pp 12502–12510

Anti-PD-1, Blockade and Systemic Photobleaching Produce Long-Term Survival in Mice With Metastatic Glomer

Zeng et al. 2013
Potential of ablative therapies to activate immune cells

Chu & Dupuy: Nat Rev Canc, 2014

RF Ablation Increases T Cell Infiltration Into Tumor Tissues

Wissniowski et al., Cancer Research, 2003; 63: 6496-500

RF Ablation alters immune infiltrate

Shi et al, 2016 Clin Canc Res
**RFA + anti-PD-1 (CT26 tumor model)**

Shi et al, 2016 Clin Canc Res

**HIFU scan strategies impact systemic immune response**

Liu et al, J Trans Med 2010

**Overview of described immune effects after HIFU in animal studies**

The Importance of Dosimetry Standardization in Radiobiology
Marc Desrosiers, Larry DeWerd, James Deye, Patricia Lindsay, Mark K. Murphy, Michael Mitch, Francesca Macchiarini, Strahinja Stojadinovic, and Helen Stone. Journal of Research of the National Institute of Standards and Technology, 2013

1) Radiation equipment and methods are increasing in variety and complexity.
2) Radiation biologists rarely receive training in radiation dosimetry.
3) Radiation biologists usually use irradiation equipment dedicated to research that is not shared with and calibrated by their clinical colleagues.
4) Radiobiologists now rarely work with radiation physicists as part of their joint routine duties, and there are fewer radiation physicists who are trained in the unique characteristics of the equipment used and problems involved in performing dosimetry in support of radiation biology.

As with the collaboration between the biologist and statistician, which aids in determining the required sample size of the experiments, the biologist-physicist collaboration can aid in determining the accuracy and precision required by a given experimental design and the methods needed to achieve these.

A growing awareness of problems in reproducibility of pre-clinical research, including cancer research editors. Requiring better reporting of animal studies will raise awareness of the importance of rigorous study design to accelerate scientific progress.
The "cancer-immune set point"

Chen & Mellman, Nature 2017

Thank you!

QUESTIONS?